CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

Current landscape of immunotherapy in the treatment of solid tumours, with future opportunities and challenges

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ABSTRACT

Immunotherapy has emerged as a new standard of care, showing survival benefit for solid tumours in multiple disease sites and indications. The survival improvements seen in diseases that were highly resistant to traditional therapies, with a poor prognosis, are unprecedented. Although the benefits observed in clinical trials are undeniable, not all patients derive those benefits, leading to emerging combination strategies and an ongoing quest for biomarker selection. Here, we summarize the current evidence for immunotherapy in the treatment of solid tumours, and we discuss emerging strategies at the forefront of research. We discuss future challenges that will be encountered as experience and knowledge continue to expand in this rapidly emerging field.

Key Words Immuno-oncology

Curr Oncol. **2018 Oct;25(5):e373-e384** **www.current-oncology.com**

INTRODUCTION

Harnessing the body's ability to mount an immune response against tumour cells is now a well-established strategy to treat cancers. For many years, it has been known that the immune system can help to treat cancer; however, initial attempts to utilize its potential did not translate into widespread use. Recently, interest in this strategy has been increasing as a result of the great successes seen in melanoma, non-small-cell lung cancer (NSCLC), and genitourinary cancers, among others. As understanding of the interaction between tumours and the immune system increases, novel therapies with sophisticated mechanisms of action are becoming standards of care. Here, we review the immunotherapies currently available to treat cancer, the emerging strategies, and the practical implications as evidence is translated into clinical practice.

SUMMARY OF CURRENT THERAPIES

In recent years, a number of practice-changing clinical studies have reported on immunotherapies. Since the initial success of ipilimumab in metastatic melanoma, immune checkpoint inhibitors have changed the landscape of systemic therapy for advanced disease in many solid tumour types. Table I summarizes key phase III studies in many cancer subtypes, including lung, head-and-neck, renal, urothelial, and gastric cancers and melanoma.

Melanoma has a long history of response to immune manipulations and its immunotherapies are now at the forefront of approved strategies and those in clinical trials. Interleukin 2, a cytokine that affects the cytotoxic functioning of T cells and the maintenance of T regulatory cells, was one of the first immunotherapies to be used in advanced disease[21]. Although response rates were modest, durable responses were observed, suggesting the possibility that some patients were "cured." However, widespread use of interleukin 2 was limited by significant toxicity. Ipilimumab was the first checkpoint inhibitor to demonstrate a survival benefit in metastatic melanoma (Table I)[1]. Ipilimumab is a fully humanized immunoglobulin G monoclonal antibody that prevents the CTLA-4 protein from binding its ligand, with the net result of preventing its inhibitory effect on T-cell activation. Building on those results, anti–PD-1 antibodies were developed as the next immune checkpoint blocking agents, and those agents have continued to improve outcomes, with less toxicity. The PD-1 receptor protein, expressed on T cells, B cells, and natural killer cells, binds to its ligand (PD-L1), expressed on stromal and tumour cells, to downregulate the immune response.

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TABLE I Summary of immunotherapy trials leading to approvals by the U.S. Food and Drug Administration and Health Canada in metastatic solid tumours

Disease site, agent, and line	Reference	Regimen	Outcome
Melanoma			
Ipilimumab			
First line			
	Robert *et al.*, 2011[1]	Ipilimumab (3 mg/kg) plus dacarbazine vs. dacarbazine	mOS: 11.2 vs. 9.1 months (HR: 0.72; $p<0.001$)
Second line			
	Hodi *et al.*, 2010[2]	Ipilimumab vs. gp100 antigen	mOS: 10 vs. 6.4 months (HR: 0.68; $p<0.001$)
Pembrolizumab			
First line	Robert *et al.*, 2015[3] (KEYNOTE-006)	Pembrolizumab (10 mg/kg every 2 or 3 weeks) vs. ipilimumab (3 mg/kg every 3 weeks)	1-Year OS: 74.1% vs. 58.2% (HR: 0.63; $p=0.0005$)
Second line	Ribas *et al.*, 2015[4] (KEYNOTE-002)	Pembrolizumab (10 mg/kg) vs. chemotherapy	**(**measure?**)**: 14.7 vs. 11.0 months
Nivolumab			
First line	Robert *et al.*, 2015[5] (CheckMate 066)	Nivolumab (3 mg/kg) vs. dacarbazine	1-Year OS: 72.9% vs. 42.1% (HR: 0.42; $p<0.001$) Updated 2-year OS: 5.5% vs. 26.7%
Nivolumab plus ipilimumab			
First line	Larkin *et al.*, 2015[6] (CheckMate 067)	(A) Nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) every 3 weeks (B) Nivolumab (3 mg/kg) (C) Ipilimumab (3 mg/kg)	mPFS: 11.5 vs. 6.9 vs. 2.9 months [HR (A vs. C): 0.42; $p<0.001$] Updated OS (AACR 2017): NR vs. NR vs. 20.0 months [HR (A vs. C): 0.55]
Non-small-cell lung cancer			
Nivolumab			
Second line	Brahmer *et al.*, 2015[7] (CheckMate 017, SCC)	Nivolumab (3 mg/kg) vs. docetaxel	mOS: 9.2 vs. 6.0 months (HR: 0.59; $p<0.001$)
	Borghaei *et al.*, 2015[8] (CheckMate 057, non-SCC)	Nivolumab (3 mg/kg) vs. docetaxel	mOS: 12.2 vs. 9.4 months (HR: 0.73; $p=0.002$)
Pembrolizumab			
First line	Reck *et al.*, 2016[9] (KEYNOTE-024, PD-L1≥50%)	Pembrolizumab (200 mg) vs. platinum-based chemotherapy	mPFS: 10.3 vs. 6.0 months (HR: 0.50; $p<0.001$)

TABLE I Continued

Disease site, agent, and line	Reference	Regimen	Outcome
Non-small-cell lung cancer continued			
Pembrolizumab Second line	Herbst *et al.*, 2016[10] (KEYNOTE-010, excluded PD-L1<1%)	Pembrolizumab [(A) 2 mg/kg or (B) 10 mg/kg] (C) Docetaxel	mOS: (A) 10.4 vs. (B) 12.7 vs. (C) 8.5 months [HR (B vs. C): 0.61; p<0.001]
Atezolizumab Second line	Rittmeyer *et al.*, 2017[11] (OAK)	Atezolizumab vs. docetaxel	mOS: 13.8 vs. 9.6 months (HR: 0.73; p=0.0003)
Head-and-neck cancer			
Nivolumab Second line	Ferris *et al.*, 2016[12] (CheckMate 141)	Nivolumab vs. treatment of physician's choice	mOS: 7.5 vs. 5.1 months (HR: 0.7; p=0.01)
Pembrolizumab Second line	Seiwert *et al.*, 2016[13] (KEYNOTE-012)	Pembrolizumab	ORR: 16% CR: 5%, with a durable response >6 months in 82% of responders
Urothelial cancer			
Atezolizumab Second line	Powles *et al.*, 2014[14]	Atezolizumab	ORR: 46% (PD L1 IHC 2/3) mPFS: 24 weeks (PD-L1 IHC 2/3)
Nivolumab Second line	Sharma *et al.*, 2017[15] (CheckMate 275)	Nivolumab (2 mg/kg)	RR: 19.6% (28.4%, PD-L1>5%; 23.8%, PD-L1>1%; 16.1%, PD-L1<1%)
Pembrolizumab Second line	Bellmunt *et al.*, 2017[16] (KEYNOTE-045)	Pembrolizumab vs. chemotherapy	mOS: 10.3 vs. 7.4 months (HR: 0.73; p=0.002)
Durvalumab Second line	Powels *et al.*, 2017[17]	Durvalumab	6-Month PFS: 24%; 1-Year PFS: 17% mOS: 14.1 months
Renal cell carcinoma			
Nivolumab Second line	Bellmunt *et al.*, 2017[16] and Motzer *et al.*, 2015[18] (CheckMate 025)	Nivolumab (3 mg/kg) vs. everolimus	mOS: 25.0 vs. 19.6 months (HR: 0.73; p=0.002)

TABLE I Continued

Disease site, agent, and line	Reference	Regimen	Outcome
Gastric cancer			
Nivolumab			
Second line	Kang *et al.,* 2017[19] (ONO-4538-12, abstract)	Nivolumab (3 mg/kg) vs. placebo	mOS: 5.32 vs. 4.14 months (p<0.001)
Merkel cell carcinoma			
Avelumab			
Second line	Kaufman *et al.,* 2016[20]	Avelumab (10 mg/kg) every 2 weeks	ORR: 31.8% (95% CI: 21.9 to 43.1) Response >6 months in 86% responders

mOS = median overall survival; HR = hazard ratio; OS = overall survival; mPFS = median progression-free survival; AACR = American Association for Cancer Research; NR = not reached; SCC = squamous cell carcinoma; ORR = objective response rate; IHC = immunohistochemistry; RR = relative risk; CI = confidence interval.

Pembrolizumab and nivolumab, two anti–PD-1 antibodies, have both been associated with survival benefits in second-line therapy for melanoma and, subsequently, in first-line therapy as single agents (Table I). More recently, in the CheckMate 067 study, a combination strategy was used, comparing nivolumab–ipilimumab with either agent alone in previously untreated patients. The study showed that, compared with either agent alone, the combination was associated with significantly higher rates of overall response and progression-free survival (PFS)[6]. The same observation was made for overall survival (OS) in a recent update[22]. Currently, the ongoing KEYNOTE-029 study is examining the combination pembrolizumab–ipilimumab in the first line, with early results demonstrating a manageable toxicity profile and an overall response rate of 53%[23].

Success with anti–PD-1/PD-L1 antibodies has since been seen in many other common solid tumours. In metastatic NSCLC, nivolumab, pembrolizumab, and atezolizumab have each demonstrated survival benefit in the second line, with pembrolizumab demonstrating a survival benefit in the first line for PDL-1–positive (≥50%) NSCLC. However, compared with standard chemotherapy, the first-line study with nivolumab did not demonstrate a survival benefit. The reason for the discrepancy is uncertain. Selection of PD-L1 expression greater than 50% in the pembrolizumab study (compared with greater than 5% in the nivolumab study) and issues with biomarker testing in the nivolumab trial have been postulated as possible explanations. In advanced renal cell carcinoma (RCC), checkpoint inhibitors have been associated with significant improvement in outcomes, with the phase III CheckMate 025 study demonstrating a survival benefit for second-line treatment with nivolumab[18].

Immunotherapies have also had significant effects in tumour sites that previously had few available treatment options beyond first-line therapy. Head-and-neck squamous cell carcinoma is characterized by genetic instability, infection with the human papillomavirus, and immune defects, making it a good candidate for immune-based treatments. The CheckMate 141 trial showed benefit with immunotherapy for recurrent or metastatic head-and-neck squamous cell carcinoma with disease progression on or after platinum therapy[12] (Table I). Pembrolizumab also showed efficacy in patients with recurrent or metastatic head-and-neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy. Its accelerated approval was based on the tumour response rate and durability of response seen in the KEYNOTE-012 study (Table I). In a phase IA expansion trial in previously treated metastatic urothelial cancer, atezolizumab was shown to lead to a median PFS of 24 weeks in patients with PD-L1 expression of 2–3 on immunohistochemistry[14]. More recently, nivolumab, pembrolizumab, and durvalumab have all gained U.S. Food and Drug Administration and Health Canada approval for the second-line treatment of urothelial cancer (Table II). In gastroesophageal cancer, the phase III ONO-4538 study presented at the 2017 Gastrointestinal Cancers Symposium showed that nivolumab in the second line or beyond for metastatic gastric cancer improved survival to 5.32 months from 4.14 months with placebo, reducing the risk of death by 37% [hazard ratio (HR): 0.63; $p < 0.0001$][19]. In pretreated advanced malignant mesothelioma, the phase II MAPS2 study demonstrated, after 15 months of follow-up, an impressive median OS of 13.6 months in patients receiving nivolumab; moreover, median OS was still not reached in patients receiving ipilimumab–nivolumab[24].

EMERGING STRATEGIES

Combination Therapy

Expression of PD-L1 is known to be a dynamic phenomenon that occurs as a result of tumour cell interaction with immune cells in the tumour microenvironment. Thus, combination treatments that lead to increased expression of PD-L1 with PD-1/PD-L1 checkpoint inhibition, and other potentially synergistic immune strategies, are being explored to induce successful antitumour immune responses. Table III summarizes phase III clinical trials to date that have investigated a combination strategy.

TABLE II Immunotherapies currently approved the U.S. Food and Drug Administration and Health Canada

Class and drug	Approved indication and date			
	Canada		United States	
Cytokine				
Interferon alfa	Melanoma	Jun 2012	Melanoma	Apr 2011
Interleukin 2			Renal cell carcinoma: metastatic	1992
Vaccine				
Sipuleucel-T			Prostate cancer: Asymptomatic or minimally symptomatic metastatic disease	Oct 2010
BCG vaccine	Bladder cancer: superficial	May 2013	Bladder cancer: superficial	Feb 2009
Oncolytic virus				
T-VEC			Melanoma: Unresectable cutaneous, subcutaneous, nodal lesions after initial surgery for intratumoural lesions	Oct 2015
Checkpoint inhibitor				
Anti-CTLA-4				
Ipilimumab	Melanoma: unresectable or metastatic after failure of, or intolerance to, other therapy	Mar 2012	Melanoma: unresectable or metastatic	March 2011
Anti-PD-L1				
Atezolizumab	Urothelial cancer: locally advanced and metastatic	Apr 2017	Urothelial cancer: metastatic breakthrough therapy designation, accelerated approval	May 2016
			NSCLC: metastatic breakthrough therapy	Jun 2016
Avelumab			Merkel cell carcinoma: metastatic disease, first line or beyond	Mar 2017
			Urothelial cancer: locally advanced or metastatic, progressed during or after platinum-containing chemotherapy	May 2017
Durvalumab	Urothelial cancer: locally advanced or metastatic, progressed during or after platinum-containing chemotherapy	Nov 2017	Urothelial cancer: locally advanced or metastatic progressed during or after platinum-containing chemotherapy	May 2017
			NSCLC: locally advanced unresectable disease that has not progressed after platinum-based chemoradiation therapy	Jul 2107
Anti-PD1				
Pembrolizumab	Melanoma: unresectable or metastatic before ipilimumab, and disease progression after ipilimumab, and if *BRAF* V600E mutation–positive, after a BRAF or MEK inhibitor	Jun 2016	Melanoma: unresectable or metastatic after progression on ipilimumab, and if *BRAF* V600E mutant, a BRAF inhibitor expanded to initial treatment	Sep 2014
	NSCLC: first line (PD-L1 expression ≥50%), no EGFR or ALK mutation	Apr 2016	NSCLC: first line (PD-L1 expression ≥50%), no *EGFR* or *ALK* mutation	Oct 2016
	NSCLC: second line (PD-L1 >1%), EGFR or ALK mutation progressing on targeted agent		NSCLC: first line in combination with pemetrexed and carboplatin for previously untreated metastatic nonsquamous disease	May 2017
	Urothelial cancer: locally advanced or metastatic, progressed during or after platinum-containing chemotherapy		NSCLC: second line (PD-L1 >1%), *EGFR* or *ALK* mutated progressing on targeted agent	Oct 2015
			Head and neck: recurrent or metastatic squamous cell carcinoma after progression on platinum-containing chemotherapy	Aug 2016
			Urothelial cancer: locally advanced or metastatic, progressed during or after platinum-containing chemotherapy	May 2017

TABLE II Continued

Class and drug	Approved indication and date			
	Canada		United States	
Checkpoint inhibitor				
Nivolumab	Renal cell carcinoma: advanced or metastatic clear cell renal carcinoma after prior antiangiogenic therapy	Apr 2016	Renal cell carcinoma: advanced or metastatic after antiangiogenic therapy	Nov 2015
	NSCLC: locally advanced or metastatic with disease progression on or after platinum-based chemotherapy; patients with *EGFR* or *ALK* aberrations should also receive targeted therapy	Feb 2016	NSCLC: squamous and nonsquamous metastatic disease after progression on first-line chemotherapy	Mar 2015
	Head and neck: recurrent or metastatic, progressing on or after platinum-based treatment	May 2017	Head and neck: recurrent or metastatic progressing on or after platinum-based treatment	Nov 2016
			Urothelial cancer: locally advanced or metastatic, progressing on platinum-containing chemotherapy	Feb 2017

BCG = bacillus Calmette–Guérin.

Increasing evidence now supports activation of the immune system as one of the contributing mechanisms of effect for cytotoxic chemotherapy. Cell death and subsequent antigen release is postulated to lead to immune stimulation, priming the tumour for immune-mediated therapies. That hypothesis provides the rationale for several studies that have combined immune agents with chemotherapy. Available phase II evidence in lung cancer demonstrates that a phased approach in which chemotherapy is administered before a checkpoint inhibitor is introduced leads to better outcomes. The KEYNOTE-021 phase II study showed that pembrolizumab combined with carboplatin and pemetrexed is tolerable and associated with improved PFS in treatment-naïve patients with nonsquamous NSCLC[28]. That finding supports the hypothesis that, when cell death caused by cytotoxic agents "releases antigens," immune response with subsequent immune checkpoint blockade is enabled. In addition, the phased approach is associated with a more favourable toxicity profile. Yet despite the promising phase II studies, a phase III study of combination chemotherapy with ipilimumab for extensive-stage small-cell lung cancer failed to show a benefit in OS or in any secondary endpoint[25,29].

Combining anti-CTLA-4 and anti–PD-1 therapies has been shown to be associated with meaningful survival improvements, and combinations are being actively studied in multiple tumour sites (Table III). Inhibition of CTLA-4 activates T-cell immune responses, leading to a potentially synergistic effect with PD-1/PD-L1 inhibitors. At the 2017 meeting of the American Association for Cancer Research, early OS data from the CheckMate 067 study examining nivolumab–ipilimumab compared with either agent used singly in metastatic melanoma were presented. Compared with ipilimumab, the combination was associated with a 45% reduction in the risk of death (HR: 0.55; $p < 0.0001$), and compared with nivolumab, a 12% reduction was observed (HR: 0.99; p = non-significant). That lack of statistical significance in survival could have been a result of patients in the monotherapy arm being treated with active agents such as ipilimumab in the second-line setting. Although combination strategies are effective, significant toxicities are also observed with their use, particularly when anti-CTLA-4 or cytotoxic agents are included. The CheckMate 012 study looked at the safety and tolerability of an alternative lower dose for ipilimumab when combined with nivolumab in patients with NSCLC, ultimately moving to a dose of 1 mg/kg every 6 weeks from the 3 mg/kg dose used for the phase III CheckMate 227 study. Similar dosing was used in the phase III CheckMate 214 study (Table III) and, overall, was well tolerated.

Not all tumour sites have seen success with single-agent immune checkpoint blockade. In a phase III study, ipilimumab failed to demonstrate benefit compared with placebo in metastatic castrate-resistant prostate cancer[30]. Combining the immune checkpoint inhibitors with cancer vaccines could, however, be a potential strategy to overcome that barrier. A phase I study combining GVAX (Aduro Biotech, Berkeley, CA, U.S.A.), a vaccine made using allogeneic tumour cells transfected with granulocyte-macrophage colony–stimulating factor, with ipilimumab showed responses in the level of prostate-specific antigen, with a tolerable side-effect profile[31]. In another phase I study, PROSTVAC (Bavarian Nordic, Kvistgaard, Denmark) was combined with increasing doses of ipilimumab, again demonstrating responses in the level of prostate-specific antigen. Success with the GVAX vaccine has also been seen in pancreatic cancer. In a phase II study, OS was improved to 9.7 months from 4.6 months when GVAX was combined with CRS-207 (live attenuated *Listeria monocytogenes* expressing mesothelin)[32]. Toxicity associated with that approach also appears to be favourable, with 20% of patients experiencing grade 3 or 4 toxicities, as opposed to the 50% or more seen with combinations of ipilimumab and PD-1 inhibitor. Table IV shows select vaccine combination studies that are currently underway for solid tumours.

TABLE III Phase III combination studies with immune checkpoint inhibitors

Reference (trial name)	Disease	Regimen	Outcome	Toxicity
Robert *et al.*, 2011[1]	Metastatic melanoma, first line	Dacarbazine plus ipilimumab vs. dacarbazine	mOS: 11.2 vs. 9.1 months (HR: 0.72; p=0.001)	Grades 3–4 toxicity: 56.3% vs. 27.5% (p<0.001)
Larkin *et al.*, 2015[6] (CheckMate 067)	Metastatic melanoma, first line	Nivolumab plus ipilimumab vs. nivolumab vs. ipilimumab	mPFS: 11.5 vs. 6.9 (p<0.001) vs. 2.9 (p<0.001) months PD-L1–positive: 14.0 months (combination and nivolumab) PD-L1–negative: 11.2 vs. 5.3 months (combination vs. nivolumab)	Grades 3–4 toxicity: 55% vs. 27.3% vs. 16.3% Adverse events leading to discontinuation: 35.4% vs. 14.8% vs. 7.7%
Reck *et al.*, 2016[25]	Early-stage SCLC, first line	Etoposide–platinum plus ipilimumab vs. etoposide–platinum	mOS: 11.0 vs. 10.9 months (NS) mPFS: 4.6 vs. 4.4 months (NS)	
Escudier *et al.*, 2017[26] (CheckMate 214)	Metastatic RCC, first line	Nivolumab plus ipilimumab vs. sunitinib	mPFS: 11.6 vs. 8.4 months (p=0.0331) mOS: NR vs. 26 months (p<0.0001) in poor- and intermediate-risk patients	Grades 3–5 toxicity: 46% vs. 63%
Motzer *et al.*, 2018[27] (IMmotion151)	Metastatic RCC, first line	Atezolizumab plus bevacizumab vs. sunitinib	mPFS, PD-L1–positive (>1% expression): 11.2 vs. 7.7 months (p=0.02) mPFS, PD-L1–negative: 11.2 vs. 8.4 months (p=0.02)	Grades 3–4 toxicity: 40% vs. 54%

mOS = median overall survival; HR = hazard ratio; mPFS = median progression-free survival; SCLC = small-cell lung cancer; NS = nonsignificant; RCC = renal cell carcinoma; NR = not reached.

TABLE IV Select studies of cancer vaccine combinations currently underway

Name	ClinicalTrials.gov ID	Status
GVAX pancreas vaccine (with CY) and CRS-207 with or without nivolumab	NCT02243371	Active, not recruiting
Multiple class I peptides and montanide ISA 51 VG with escalating doses of anti–PD-1 antibody BMS936558	NCT01176461	Active, not recruiting
Study of nivolumab in combination with GM.CD40L vaccine in adenocarcinoma of the lung	NCT02466568	Withdrawn
Vaccine therapy and pembrolizumab in treating patients with hormone-resistant, metastatic prostate cancer	NCT02499835	Recruiting
Nivolumab with DC vaccines for recurrent brain tumours	NCT02529072	Active, not recruiting
Immunization strategy with intra-tumoural injections of Pexa-Vec with ipilimumab in metastatic or advanced solid tumours	NCT02977156	Recruiting
A Phase I/II trial to evaluate a peptide vaccine plus ipilimumab in patients with melanoma	NCT02385669	Recruiting

Early Disease

To date, most of the evidence to support immune-based therapies has been developed in advanced or metastatic disease. In melanoma, before the introduction of immune checkpoint inhibitors, immune therapy in the form of interferon alfa-2b was considered a standard therapy option for patients with high-risk resected disease[33–35]. Although a benefit in disease-free survival was seen, no os benefit was observed. More recently, ipilimumab was shown to have both relapse-free survival and os benefit when compared with placebo in the European Organisation for Research and Treatment 18071 trial in stage III cutaneous melanoma. Relapse-free survival was significantly better (5-year rate: 18.3% vs. 38.9%), and os was prolonged (5-year rate: 65.4% vs. 54.4%)[36]. However, rates of toxicity were high, with adverse events of any grade being observed in 98.7% of patients, and grade 3 or 4 events in 54.1%. Only 29% of patients were able to complete more than 1 year of therapy. Currently, two adjuvant studies in high-risk disease that have completed accrual are awaiting results: the Eastern Cooperative Oncology Group 1609 trial comparing ipilimumab with interferon alfa-2b as adjuvant treatment in high-risk disease (see NCT01274338 at http://ClinicalTrials.gov/), and the CheckMate 238 trial comparing ipilimumab with nivolumab (NCT02388906). Another study is underway to

examine nivolumab and pembrolizumab for the adjuvant treatment of melanoma (NCT02362594).

In other tumour sites, trials are currently underway to assess the role for immune-based agents in the curative setting. The PACIFIC study, which is evaluating 1 year of durvalumab after curative-intent chemoradiation in patients with stage III NSCLC, showed an increase in PFS to 16.8 months from 5.6 months (HR: 0.52; 95% confidence interval: 0.42 to 0.65)[37]. In a separate study, nivolumab was shown to be safe and feasible in early-stage NSCLC in the neoadjuvant setting. Before surgical resection, patients with stages I–IIIA NSCLC ($n = 18$) received doses of nivolumab at 4 weeks and then at 2 weeks. In 7 patients (39%), major pathologic responses (<10% residual viable tumour) were associated with immune infiltration of the tumour. One patient experienced a complete pathologic response[38]. Neoadjuvant strategies are also being examined in multiple tumour sites, but questions about the optimal strategy remain. Whether dual checkpoint blockade would be more effective in the neoadjuvant setting is unclear.

PRACTICAL CONSIDERATIONS

Response Criteria

The patterns of response observed with immunotherapy agents might be different from those observed with traditional cytotoxic chemotherapeutics or molecularly targeted agents. Patients might experience a transient worsening of disease that would be characterized as progression by traditional response criteria, followed by stability or improvement. Compared with the response to cytotoxic therapies, responses to immunotherapies can also take longer to become clinically apparent and can be durable well beyond the induction period. Hypotheses as to why this "pseudoprogression" occurs include the homing of cytotoxic T lymphocytes into the tumour; increase of the inflammatory milieu, causing a transient enlargement of the tumour mass and associated regional lymph nodes; and fast-growing tumours, which might increase in size before the treatment effect begins[39].

This situation made it imperative that a separate set of criteria for evaluating immune response be used in trials of efficacy to avoid early discontinuation of a potentially effective agent. Wolchok *et al.*[39] thus proposed new immune-related response criteria (IRRC) to accurately and reproducibly measure the efficacy of immune agents (Table V). The criteria are based on three main principles. First, rather than target lesions, total tumour burden is used to determine quantity of disease. Second, confirmation at least 4 weeks after first documentation of any response other than stable disease is required. Finally, new lesions do not necessarily represent progressive disease. Instead, those lesions are included into the whole tumour burden, and their significance depends on confirmation. For instance, in an analysis of KEYNOTE-001 evaluating pembrolizumab in metastatic melanoma, atypical responses were observed. A comparison of the IRRC with the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) showed that, based on survival analysis, RECIST might underestimate benefit in approximately 15% of patients[40]. In a further effort to standardize evaluation in clinical trials, the immune RECIST (iRECIST) was written based on expert opinion and consensus, including all available knowledge about response dynamics[41]. The iRECIST also incorporates pseudoprogression and allows for new lesions (standard RECIST version 1.1 does not). The new criteria remain to be validated; they are still being created based on the initial trial data currently being collected.

Certain challenges in using the IRRC remain, however. Tumour burden is based on the sum of the products of all target lesions (World Health Organization criteria, in which the product of the longest measured perpendicular diameter is used for each target lesion), which has high inter-observer variability in practice. Additionally, the new criteria were developed based on responses to anti-CTLA-4 and anti–PD-1/PD-L1 monoclonal antibodies in malignant melanoma. Those drugs promote an adaptive response through clonal expansion of CD4+ or CD8+ lymphocytes, which supports massive infiltration as the source of pseudoprogression[42]. In a cohort of 56 patients with advanced NSCLC treated with nivolumab alone, responses were noted in the same 8 patients whether IRRC or RECIST 1.1 was used, and no case of pseudoprogression was noted[43]. Whether the IRRC is or is not as important in the context of other immune-based therapies with alternative mechanisms of action is not clear.

Predictors of Response to Immune-Based Therapy

Although the benefits of immune-based therapies have been significant, the fact remains that only a portion of patients derive benefit. How best to select those patients has yet to be determined.

The biomarker that has been the most broadly studied is PD-L1 expression (in trials of PD-1/PDL-1 checkpoint inhibitors). Although using PD-L1 expression intuitively makes sense, several limitations are associated with this biomarker. Expression of PD-L1 and PD-1 is dynamic, and it changes in relation to local cytokines and other factors, including prior systemic therapies. Additionally, the threshold that separates "positive" from "negative" is variable depending on the analysis, and the different assays that measure expression yield discordant results[44]. Overall, however, most trials evaluating PD-L1 status show trends of increasing response rates with increasing expression[5,6,45].

The utility of PD-L1 as a predictive biomarker has been most consistent with pembrolizumab in the setting of lung cancer. Currently, PD-L1 immunohistochemistry staining is the only diagnostic approved by the U.S. Food and Drug Administration for patients with NSCLC treated with pembrolizumab and, based on the inclusion criteria in KEYNOTE-024, that staining has to be 50% or greater in patients treated in the first line. With nivolumab, the relationship has been less clear. A correlation was demonstrated in CheckMate 057, which evaluated nivolumab in the second line for nonsquamous NSCLC, but CheckMate 017 (for squamous NSCLC) showed no relationship between the various PD-L1 positivity cut-offs (1%, 5%, or 10%) and response rate, PFS, or OS[7,8]. However, in the study evaluating combined ipilimumab–nivolumab in the first line for NSCLC, a predictive utility of PD-L1 was observed. In patients with PD-L1–positive tumours, nivolumab alone was equivalent to the combination, with a median PFS of

TABLE V Comparison between World Health Organization (WHO) criteria and the immune-related response criteria (irRC)[39]

Variable	Applicable criteria	
	WHO	irRC
New, measureable lesions[a]	Always represent progressive disease	Incorporated into tumour burden
New, non-measurable lesions[b]	Always represent progressive disease	Do not define progression (but preclude immune-related complete response)
Non-index lesions	Changes contribute to defining best overall response of complete response, partial response, stable disease, or progressive disease	Contribute to defining immune-related complete response (complete disappearance required)
Complete response	Disappearance of all lesions in 2 consecutive observations not less than 4 weeks apart	Disappearance of all lesions in 2 consecutive observations not less than 4 weeks apart
Partial response	≥50% Decrease in the sum of products of diameters of all index lesions compared with baseline in 2 observations at least 4 weeks apart, in absence of new lesions or unequivocal progression of non-index lesion	≥50% Decrease in tumour burden compared with baseline in 2 observations at least 4 weeks apart
Stable disease	50% Decrease in the sum of products of diameters compared with baseline cannot be established, nor a 25% increase compared with nadir in the absence of new lesions, or equivocal progression of non-index lesions	50% Decrease in tumour burden compared with baseline cannot be established, nor a 25% increase compared with nadir
Progressive disease	Any or all of at least a 25% increase in the sum of products of diameters compared with nadir, or unequivocal progression of non-index lesions, or appearance of new lesions (at any single time point)	At least 25% increase in tumour burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart

[a] ≥5×5 mm.
[b] <5×5 mm.

14.0 months in both arms. In contrast, the combination was superior in PD-L1–negative patients, reaching a median PFS of 11.2 months compared with 5.23 months for nivolumab alone, thus identifying a potential biomarker for the group that benefits from combination therapy.

Based on the inconsistency observed with PD-L1, alternative biomarkers are being sought to predict response to therapy. Clonality of T-cell receptors has been explored—specifically, the association between CD8 and PD-1/PD-L1 expression. Expression of CD8+, PD-1, and PD-L1 was significantly associated with response to pembrolizumab treatment in patients with metastatic melanoma[46]. Those findings were supported in a study of patients with muscle-invasive bladder cancer, which found a correlation between a greater number of somatic mutations and a lower T-cell receptor diversity index. Those tumours had a greater CD8+:FOXP3 ratio, indicating specific CD8+ clonal expansion and antitumour immune responses.

Emerging data support the hypothesis that tumour mutational burden (TMB) and genomic instability lead to higher responses to immune therapies. In NSCLC, smoking history is correlated with increased mutational burden[47] and has been shown to correlate with increased rates of response to PD-L1 inhibitors[48]. In a more recent study, whole-exome sequencing of patients with NSCLC treated with pembrolizumab revealed an association between TMB and improved overall response rate, PFS, and durable clinical benefit[48]. Tumours reliant on only 1 driver mutation, such as *EGFR* activating mutation–positive lung cancers, have a consistently low response rate to immunomodulating agents. In an exploratory analysis that used whole-exome sequencing to look at TMB in specimens from patients enrolled in the CheckMate 026 study in NSCLC, patients with a high TMB were shown, compared with their counterparts having a low TMB, to experience superior PFS. Similar findings from the CheckMate 032 study in small-cell lung cancer were recently presented. That phase I/II study examined nivolumab compared with nivolumab–ipilimumab in previously treated metastatic disease. In both treatment arms, response rates and 1-year survival were both higher in patients with a high TMB. In a recent analysis that combined available TMB data from 27 different cancer types, a strong correlation was demonstrated between high TMB and response to checkpoint inhibition[49].

Duration of Therapy

One of the unique features of immune therapy is the durability of the responses observed. Thus, the appropriate treatment duration remains uncertain. Ipilimumab received regulatory approval for use in melanoma based on second-line studies in which the drug was given for 4 doses, with no maintenance. No randomized studies have addressed the potential role of maintenance. The 4-dose strategy was subsequently used in the studies combining ipilimumab with nivolumab for melanoma and NSCLC.

With the optimal duration of therapy for checkpoint inhibitors remaining unknown, these agents are currently given continuously until disease progression or until limiting toxicity. Updated follow-up from the KEYNOTE-010 trial of pembrolizumab in NSCLC showed that OS was maintained. In an analysis of the 47 patients who completed 2 years of pembrolizumab and stopped treatment, 90% experienced an ongoing response. Follow-up even after therapy stop showed that only 2 patients (4%) experienced

disease progression during that time, suggesting that even after therapy stops, clinical benefit can be observed. That observation was further supported by the 5-year follow-up of the phase I CA209-003 study of nivolumab in advanced NSCLC, which reported an estimated 5-year OS rate of 16%, with ongoing clinical benefit even after cessation of therapy[50]. Those studies led to the randomized CheckMate 153 study, which randomized patients with advanced NSCLC and at least 1 prior line of systemic therapy to either 1-year or continuous treatment with nivolumab. Data from the first 220 patients showed that continuous treatment is superior for PFS, with a HR of 0.42 (95% confidence interval: 0.25 to 0.71) and a trend toward superior OS (HR: 0.63). Based on those data, continuous treatment was established as the standard of care.

There remains a population of patients that might sustain benefit from a shorter duration of treatment. One proposed strategy to select those patients is to determine duration based on minimal residual disease[51]. Although data to support that approach are limited, a study in NSCLC measured PD-L1–positive circulating tumour cells (CTCs) at baseline and at 3 and 6 months. At baseline and 3 months, the presence of PD-L1–positive CTCs was found to be associated with poor patient outcomes. At 6 months after treatment, all patients who still had PD-L1–positive CTCs experienced progressive disease; those with PD-L1–negative CTCs obtained clinical benefit[52].

Economic Impact

Although the clinical benefit of immune therapies is clear, questions about the cost-effectiveness of the approach remain. In advanced melanoma, the inhibitors ipilimumab, nivolumab, and pembrolizumab have all demonstrated cost-effectiveness[53–55]. For other tumour sites, cost-effectiveness is less clear. A Canadian cost-effectiveness analysis of nivolumab compared with docetaxel or erlotinib as second-line therapy for NSCLC showed that nivolumab cost, respectively, an additional $151,560 or $140,601 per quality-adjusted life-year[56].

In a recent review article by Tartari *et al.*[57], the per-patient estimated costs for pembrolizumab and nivolumab were estimated for melanoma, NSCLC, and RCC. To calculate the per-patient cost, the cost of each drug per milligram was used to determine a monthly cost (based on a weight of 70 kg). Pembrolizumab was estimated, based on dose and schedule, to cost $23,017 and $20,716 per patient per month in melanoma and NSCLC respectively. Nivolumab was estimated to cost $12,682, $12,600, and $6,984 per patient per month in melanoma, NSCLC, and RCC respectively. Using the median PFS from the clinical trials and the World Health Organization's estimate of new cases worldwide per annum, the annual cost was calculated. For pembrolizumab, that total reached $3.8 billion in melanoma and $83.9 billion in NSCLC for 1 year. For nivolumab, the total cost was $1.7 billion, $27.3 billion, and $2.7 billion for melanoma, NSCLC, and RCC respectively. That study highlights the paradox for successful immunotherapeutics, which become less cost-effective as the duration for which they are required lengthens. It also clearly reveals the effect of disease incidence, with NSCLC having a significantly higher incidence than either melanoma or RCC.

CONCLUSIONS

Immunotherapies are currently revolutionizing the treatment of solid tumours. In a series of practice-changing trials, they have delivered meaningful survival improvements for patients with (previously) poor-prognosis cancers and for certain cancer types in which therapeutic options were limited. Many aspects of their use, including optimal combinations, sequencing, duration, and clinical setting, remain to be clarified. Ongoing clinical trials will serve to further increase their role, but careful consideration must be given to finding the safest, most individualized, and most cost-effective way to incorporate them into cancer care.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have no competing interests relevant to this article.

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